PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CU2002/0336	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CU 03/00020	International filing date *(day/month/year)* 22.12.2003	Priority date *(day/month/year)* 27.12.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/02		
Applicant CENTRO DE INGENIERIA GENETICA Y BIOTECNOLOGIA		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.05.2004	14.04.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Villa Riva, A Telephone No. +49 89 2399-8404

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CU 03/00020

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-13 as originally filed

Claims, Numbers

1-5 filed with telefax on 03.03.2005

Drawings, Sheets

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: English , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☒ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	5
	No:	Claims	1-4
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: Oliven A et al. , Pharmacology 22: 135-138 (1981)
D2: Bachmann F , The Journal of laboratory and clinical medicine,72 (2) : 228-238 (1968).
D3: SUMI H ET AL: "Activation of plasma fibrinolysis after intrarectal administration of high molecular urokinase and its derivative." ACTA HAEMAT., vol. 70, 1983, pages 289-295.
D4: US-B-4 944 943

D1 was cited in the application, D2 and D4 are cited out of the examiner's personal knowledge. Copies are annexed to the present communication, D3 was cited in the Search Report.

The amendments filed with the fax of 03.03.05 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 19(2) PCT. The amendments concerned are the following: the formulations in claims 1-5 can contain any protein or peptide with a trombolytic activity. The original documents do only disclose streptokinase in its natural or recombinant form or t-PA as peptides/proteins for the uses of the invention.

Notwithstanding the above objection, the following remarks on novelty and inventive step are drafted.

Claims 1-5 are formally novel under PCT Art. 33(1) and (2) because none of the cited documents disclose the use of rectal peptide/protein formulations for the treatment of peripheral thrombosis or haemorrhoidal disease.

D4 discloses a mixture of peptides/proteins with antithrombotic/thrombolytic properties, among which steptokinase, urokinase, t-PA (col. 1, lines 23-33). These can be used for the treatment of peripheral occlusive diseases, like thrombophlebitis and hemorrhoidal

thrombosis. The difference with the present application is that the prptides are administered parenterally.
D2, p. 229, section "Materials and Methods" , line 3, discloses the use of "Varidase rectal suppositories containing 20,000 U" of streptokinase in the comparison study with the injectable and oral formulations.
D1, p. 138, last paragraph, discloses that streptokinase, given either rectally (via an aqueous enema) or orally is not absorbed in the GI tract.
D4 discloses intrarectal administration of high molecular weight urokinase.
Therefore, the skilled person seeking for a streptokinase preparation for the local treatment of haemorrhoids without systemic effects, suitable for self-administration, and providing for a better patient compliance than parenteral use, would combine the teachings of D4 with any of D1-D3 and obtain the formulation and the uses of present claims 1-4.
These claims are not considered inventive under PCT Art. 33(1) and (3).

The presence of the specific quantity of streptokinase in claim 5, which is higher than that employed in prior art is not suggested nor disclosed by the cited prior art items. Therefore, also in view of the examples, it is considered inventive.

CLAIMS

1. The use of peptides and proteins with thrombolytic action for the manufacture of a medicament for treating occlusive peripheral vascular disease, hemorrhoid disease, in particular the occlusion of hemorrhoidal vessels and disorders associated with these diseases in a subject, by rectal route.

2. The use according to claim 1 wherein the medicament is a rectal formulation.

3. The use according to claim 1 wherein the medicament comprises peptides and proteins where at least one of the components is a clot-lytic agent.

4. The use according to claim 1 wherein the medicament contains recombinant streptokinase and pharmacologically acceptable diluent carrier or excipient for rectal route.

5. The use according to claim 4 wherein the medicament contains recombinant streptokinase in a concentration from 50 000 – 1 500 000 UI/g.